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• *BRIEF REPORTS* •

Serum IL-6, TNFα and CRP levels in Greek colorectal cancer patients: Prognostic implications

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Abstract

AIM: The significance of preoperative serum IL-6, TNFα and CRP levels in the progression of colorectal cancer (CRC) has not been fully elucidated. Our intention was to investigate their role and identify their prognostic significance.

METHODS: The IL-6, TNFα and CRP levels were measured in 74 CRC patients and the relationships between their elevations and both the clinicopathological factors and prognosis of patients were investigated. Serum concentrations of human IL-6 and TNFα were determined by enzyme-linked immunosorbent assay (ELISA). CRP was measured by an immunoturbinometric method.

RESULTS: Median IL-6, TNFα and CRP levels were significantly higher in CRC patients than in normal controls. High levels of serum IL-6, TNFα and CRP were correlated with larger tumor size. Furthermore, high IL-6 and high CRP levels were associated with reduced overall survival.

CONCLUSION: Serum IL-6, TNFα and CRP levels definitely increase in CRC patients. Pre-operative serum elevation of IL-6 and CRP was thus found to be predictor of the prognosis of CRC patients. The clinical value of TNFα in CRC needs to be further investigated.

Key words: IL-6; TNFα; CRP; Colorectal cancer

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INTRODUCTION

Colorectal cancer (CRC) represents a significant cause of morbidity and mortality worldwide. Currently available chemotherapy for the disease remains unsatisfactory, particularly in patients with advanced CRC. Previous attempts to use immune therapy to treat CRC did not seem to be very effective either[1]. The anti-tumor immune response is regulated by several factors, including cytokines produced by the tumor and other cells of tumor stroma[2]. Cytokines can modulate expression of tumor antigens, adhesion molecules and production of immunosuppressive factors by tumor cells. It is plausible that the local cytokine microenvironment, acting on the tumor cell or on the adjacent cells, can either block or facilitate tumor growth.

Cytokine regulation of human CRC is not clearly understood. However, it has been postulated that pro-inflammatory cytokines strongly influence the immunological status of CRC[3]. Among them, IL-6 and TNFα can initiate the innate immune response by inducing the acute phase of inflammation[4,5]. Additionally, IL-6 also appears to be involved in malignant transformation, tumor progression and tumor-associated cachexia, as reported in studies on Kaposi's sarcoma[6], multiple myeloma[7], renal cell carcinoma[8], prostate cancer[9], ovarian cancer[10] and breast cancer[11]. TNFα is also an important factor in the tumor microenvironment in human CRC. However, the role of TNFα in the local regulation of tumor growth is unclear. Barth *et al*[12] reported that better survival of CRC patients was associated with a larger number of TNFα expressing cells than in normal mucosa. However, TNFα may also play a negative role, favoring the growth of colorectal cancer by enhancing neo-vascularization and tumor metastases and down regulating the cell-mediated immune response by induction of soluble mediators such as IL-10[13-15].

Furthermore, C-reactive protein (CRP), a protein synthesized in the hepatocytes, has also been reported to be related both to the malignant potential of the neoplasms and to physical cachexia[16]. CRP belongs to the family of acute phase proteins, which are up regulated by cytokines, such as IL-6 and TNFα[17]. Studies in patients with colorectal cancer indicated that those with elevated serum CRP

concentrations had poorer prognoses than those whose CRP level were not increased. In addition, it has been suggested that increased CRP was associated with more frequent local tumor invasion[18], more advanced pathologic stage[19] and a higher rate of recurrence[20,21].

In light of the above, the purpose of our study was to measure the serum levels of IL-6, TNFα and CRP in Greek patients with colorectal cancer and to analyze these levels in relation to the clinicopathological findings.

MATERIALS AND METHODS

Patients

The study population consisted of 74 consecutive patients, who underwent resections for local colorectal cancer lesions, from September 2001 to September 2003 at D´Department of Surgery, Athens University Medical School. Patients with concomitant diseases (e.g., infectious diseases, inflammatory bowel disease, autoimmune conditions, allergy, asthma, *etc.*) capable of raising the serum levels of IL-6, TNFα, and/or CRP were excluded for the study. The patients ranged from 33 to 86 years of age (mean±SD: 66.83±10.45 years, mean±SE: 66.83±1.24 years) and consisted of 39 males and 35 females. All patients gave their informed consent and the hospital review board approved the study. The colorectal cancer was located in the cecum and ascending colon in 16 patients (21.62%), the transverse colon in 3 (4.05%), descending colon and sigmoid colon in 23 (31.1%), rectum in 24 (32.43%) and rectum and sigmoid colon in 8 (10.81%). The primary cancers of all patients were excised. Seventy-four patients had been followed up till April 2004 or death. The median time (±SD, ±SE) of follow-up and the follow-up range were 18.57 (±8.61, ±1.017) mo and 1-32 mo respectively.Twenty-six patients were lost to follow-up. The following parameters were recorded in all patients: age, sex, Dukes' staging[22], degree of histologic differentiation (good, moderate, or poor) and number of metastatic nodes. Serum samples from 25 sex- and age-matched normal healthy individuals were used as controls.

Serum samples

Blood samples were obtained before surgery to determine the serum concentration of IL-6, TNFα, and CRP. For all patients tumor marker serum levels [carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), cancer antigen 125 (CA 125), and tissue polypeptide antigen (TPA)] were also determined. The blood samples were centrifuged at 3 000 r/min for 5 min. Then the serum was removed and stored at -80 ℃ until biochemical analysis.

Biochemical determinations

Serum concentrations of human IL-6 were determined by enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems Inc., Minneapolis, MN). The limit of detection of the assay was 0.7 pg/mL. Because the cut-off point (ca. 8 pg/mL) was around the median value, we assigned patients with values less than 8 pg/mL to the low-level IL-6 group and those with equal or more than 8 pg/mL to the high-level IL-6 group. TNFα concentrations in sera were also determined by enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems Inc., Minneapolis, MN). The limit of detection of the assay was 0.12 pg/mL. Because the cut-off point (CA 4.71 pg/mL) was around the median value, we assigned patients with values less than 5 pg/mL to the low-level TNFα group and those with equal or more than 5 pg/mL to the high-level TNFα group. CRP was measured by an immunoturbinometric method, using a commercial kit (Dade Behring GmbH, Marburg, Germany). The serum levels ranging from 0 to 7 mg/L were normal in this assay. Because the median value was 6.79 mg/L, we defined values of less than 7 mg/L as low-level CRP and values equal to or above 7 mg/L as high-level CRP. Serum CEA, CA19-9, CA125 and TPA concentrations were determined by enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems Inc., Minneapolis, MN).

Statistical analysis

Parametric two-factor ANOVA was used to test the differences among patient specific variables with the IL-6, TNFα and CRP dichotomies as factors. These factors were compared versus patient categories in contingency table analysis, based on the chi-square distribution. The survival curves were made using the Kaplan-Meier method and comparison was with the long rank test. Correlations between examined markers were evaluated by Spearman nonparametric rank test (r). The P values obtained were 2-tailed and significant differences were assumed below $P = 0.05$. The analysis was aided by GraphPad InStat (version 3.00, GraphPad Software Inc., San Diego, CA) and SPSS v. 11 (SPSS Inc., Chicago, IL).

RESULTS

The clinicopathological characteristics of the 74 CRC patients are summarized in Table 1. Serum IL-6 levels in CRC patients (median value: 8.11 pg/mL, range 1.09-188.42 pg/mL) were significantly higher than those in normal individuals (median value: 3.52 pg/mL, range 0.45-9.96 pg/mL, $P<0.01$). Taking 8 pg/mL as the threshold level, the serum IL-6 concentration was elevated in 35 of 74 patients (47.3%). The maximum size of the tumor in the high IL-6 group (4.8±1.9 cm) was significantly larger than that in low IL-6 group (3.8±1.3 cm, $P = 0.05$). The IL-6 levels in CRC patients with lymph node involvement was 15.2±24.3 pg/mL and the levels in patients without lymph node involvement was 26.9±29.1 pg/mL. The difference was not significant. No significant correlations were found between IL-6 levels and the serum levels of CEA, CA19-9, CA125, TPA, histological type, differentiation, and Dukes' stage (Table 1). Nevertheless, patients with increased serum IL-6 concentrations showed a decrease in overall survival ($P<0.05$, Figure 1).

The serum levels of TNFα in CRC patients (median value: 4.84 pg/mL, range 1.46-292.13 pg/mL) were found notably higher than in normal subjects (median value: 2.07 pg/mL, range 0-4.71 pg/mL, $P = 0.01$). Taking 5 pg/mL as the threshold level, the pre-operative serum TNFα concentration was increased in 33 of 74 patients (44.6%). Similar to the elevated IL-6 group, the maximal tumor size in CRC patients with high TNFα concentrations (4.7±1.6 cm) was significantly larger than that in the group with low TNFα

Table 1 Clinicopathological characteristics of colorectal cancer patients associated with high and low serum IL-6, TNFα and CRP levels

	Low IL-6 <8 pg/mL (*n* = 39)	High IL-6 ⩾ 8 pg/mL (*n* = 35)	Low TNFα <5 pg/mL (*n* = 41)	High TNFα ⩾5 pg/mL (*n* = 33)	Low CRP <7 mg/L (*n* = 36)	High CRP ⩾7 mg/L (*n* = 38)
Age (yr)	66[1]	70[1,a]	69[1]	67[1]	66[1]	69[1]
Gender ratio (M:F)	19:20	20:15	21:20	18:15	16:20	23:15
Tumor location						
Cecum/ascending	7	9	7	8	6	10
Transverse	1	2	0	2	1	2
Descending/sigmoid	15	8	15	7	10	13
Rectum	10	14	10	14	13	11
Rectum/sigmoid	6	2	9	2	6	2
Differentiation						
Good	1	2	2	2	2	1
Moderate	33	26	33	26	26	32
Poor	5	7	6	5	8	5
Preoperative CEA (ng/mL)	4.3[1]	4.4[1]	4.6[1]	4.3[1]	4.8[1]	3.6[1]
Preoperative CA19-9 (ng/mL)	12[1]	9[1]	12[1]	10[1]	10[1]	12[1]
Preoperative CA125 (ng/mL)	11.9[1]	13[1]	11.9[1]	14[1]	13[1]	11[1]
Preoperative TPA (ng/mL)	42[1]	71[1]	44[1]	70[1]	42[1]	60[1]
Maximum size of tumors (cm)	3.8±1.3[a]	4.8±1.9[a,2]	3.8±1.6[2]	4.7±1.6[a,2]	3.7±1.2[2]	4.8±1.9[2,b]
Growth characteristics						
Ulcerative	12	19	25	13	15	23
Protruding	27	16	16	20	21	15
Lymph node metastasis						
Positive	21	14	23	12	18	17
Negative	18	21	18	21	18	21
Dukes' stage (%)						
A	7 (54)	6 (46)	9 (69)	4 (31)[a]	10 (67)	5 (33)[a]
B	11 (46)	13 (54)	7 (29)	17 (71)	17 (59)	12 (41)
C	19 (63)	11 (37)	20 (67)	10 (33)	8 (35)	15 (65)
D	2 (29)	5 (71)	5 (71)	2 (29)	1 (14)	6 (86)

CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; CA 125, cancer antigen 125; TPA, tissue polypeptide antigen. [1]Values are median, [a]P<0.05 *vs* controls, [2]Values are±SD, [b]P<0.01 *vs* low CRP group.

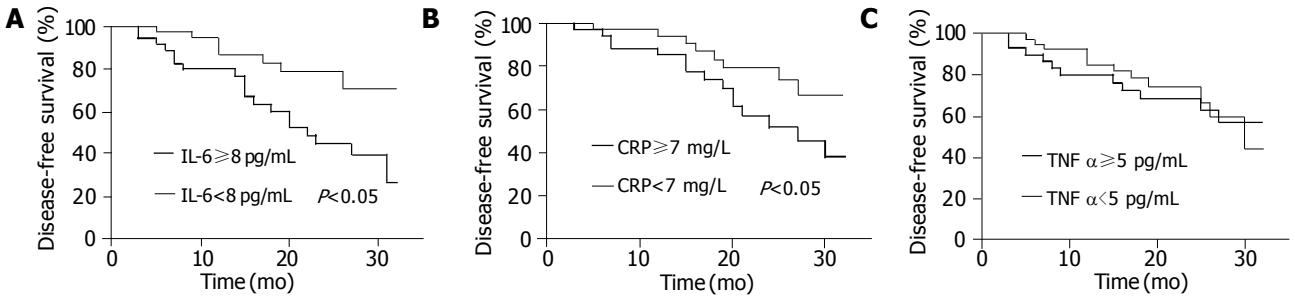

Figure 1 Overall disease-free survival of CRC patients stratified by IL-6, TNFα and CRP pre-operative serum concentrations. A: Disease-free survival in patients with IL-6<8 pg/mL; B: Disease-free survival in patients with CRP<7 mg/L; C: Disease-free survival in patients with TNFα<5 pg/mL.

levels (3.8±1.6 cm, P<0.05). Additionally, no significant difference in TNFα levels was observed between the CRC patients with lymph node involvement (6.6±8.7 pg/mL) and those without (16.7±46.2 pg/mL). The relationship of TNFα to serum level of CEA, CA19-9, CA125, TPA, histological type, differentiation, or overall survival, was not significant. Interestingly, a significant ratio of patients in stage B of Dukes' classification has showed elevated pre-operative levels of circulating TNFα (Table 1, Figure 1).

Serum CRP levels in CRC patients (median value: 6.79 mg/L, range 0.3-182 mg/L) were also elevated in CRC patients compared to the controls (median value: 3 mg/L, range 0.2-5.72 mg/L, P<0.05). Taking 7 mg/L as the threshold level, the pre-operative elevation of the serum CRP value was recognized in 38 patients (51.3%), whereas no such elevation was recognized in 36 (48.7%) patients. The maximal size of the tumors in the high CRP group (4.8±1.9 cm) was significantly larger than in the low CRP group (3.7±1.2 cm, P <0.01). As indicated in Table 1, no significant difference was observed between the proportion of histopathologically detected lymph node metastasis, differentiation, histological type, and serum levels of CEA, CA19-9 and CA125. However, TPA levels were significantly increased in the high CRP group *vs* the low CRP group (P<0.05). Notably, the ratio of stage C and D by Dukes' classification was significantly increased in the group with

elevated CRP (Table 1). The overall survival-rate in high CRP group was considerably more unfavorable than those in low CRP group ($P<0.05$, Figure 1).

Regarding quantitative associations between the examined markers, IL-6 levels were positively correlated with those of TNFα ($r = 0.55$, $P = 0.01$), and CRP ($r = 0.62$, $P = 0.01$).

DISCUSSION

Currently, there is ample literature regarding the role of various cytokines in CRC patients. IL-6 expression has been reported as secondary to a wide spectrum of malignancies and its clinical importance is being increasingly recognized[23]. In agreement with earlier studies, IL-6 levels in our CRC patients cohort were also found to be elevated[23-25].

The mechanisms leading to IL-6 induction and to IL-6 presence in high concentrations in the serum of those patients, include CEA-induced IL-6 production by Kupffer cells, malignancy-related chronic stress leading to increased IL-6 blood concentrations as well as direct IL-6 production and secretion by tumor-associated macrophages or the tumor cells themselves[23,24,26]. IL-6 appears to enhance tumorigenesis by a paracrine or autocrine mechanism and to have an inhibitory effect on the anti-tumor immune response[27]. Also the clinical significance of IL-6 pre-treatment levels has already been previously evaluated[24,25,27]. According to those authors, IL-6 concentrations reflected disease status, and were commonly associated with metastatic disease[24,25,27].

Our study, in a relatively limited number of CRC patients, failed to reveal a significant association with tumor stage. Moreover, we found that more patients with Dukes' stage C had low IL-6 levels, although the difference was not significant. However, our cohort contained only a small number of Duke's D patients. In the latter, 71% were found to have high IL-6 levels. Additionally, large tumor size correlated with elevated IL-6 levels. The aforementioned are partially consistent with previous observations that tumor burden and liver metastasis lead to higher IL-6 levels[27]. Liver metastasis may lead to hepatic dysfunction and subsequent decreased capacity for clearance of this cytokine[27]. One should not overlook the influence of different cut-off values used in the assessment of serum IL-6, as well as the ethnic origin of CRC patients in different studies.

Notwithstanding, in agreement with previous studies, serum IL-6 pre-operative levels were predictive of unfavorable prognosis with regard to CRC patients' survival[11,27,28]. Moreover, different from the prior studies, the fact that our cohort comprised more of non-metastatic stages strengthens the clinical relevance of this observation. In other words, IL-6 levels may be used as an adverse prognostic marker in the absence of advanced metastatic disease. Its independent prognostic significance, though, cannot be supported by our study since multivariant analysis was not performed due to the sample size. However, larger patients study-population and stage sub-groupings may aid in the more accurate evaluation of the cytokine's clinical significance.

TNFα has been detected in a number of different tumor types. Human epithelial tumor cells and infiltrated macrophages have been found to express TNFα protein. In certain malignancies increased production of TNFα correlated with worse prognosis[29]. On the other hand, high expression of this marker in Dukes' C CRC Japanese patients was a favorable indicator of prognosis[3]. Another study reported that, among other cytokines, TNFα was significantly elevated in stage B patients prior to surgery[30]. The latter is in keeping with our results, although a satisfactory explanation might not be easily offered. The relation to tumor- size but not other adverse histopathological variables could be related to the fact, that larger tumors may trigger a more potent immunological response manifested by the circulation of proinflammatory cytokines such as TNFα. It should be acknowledged though that the biological and clinical role of TNFα in CRC requires further elucidation.

The only parameter of the current study that demonstrated a clear association to the disease stage was CRP. It has also been suggested that an elevated pre-operative CRP may be an indicator of the malignant potential of the tumor and predictor of unfavorable prognosis in CRC patients. In accordance with the findings of Nozoe *et al*[19], our results have shown that the prognosis of patients without a pre-operative elevation of serum CRP level proved to be considerably better than that of patients with such an elevation. Tumor progression, among other pathophysiological sequelae, might lead to the development of an acute phase protein response, which is observed as an increase in CRP levels. Similar to the presently proved IL-6 prognostic significance as far as it concerns patients' overall survival, CRP elevation may be considered an unfavorable indicator. In spite of the usual clinical strategy to use tumor markers such as CEA and CA19-9 in determining disease progression, CRP may play an important role in signifying advanced disease.

Our study also shows that serum IL-6 levels are correlated with serum CRP levels. Apart from CRC, such a correlation has been observed in various malignancies[31]. IL-6 may play a critical role in controlling the production of acute phase proteins in liver cells and modulating host biological responses[27]. The observed inter-relation between IL-6 and TNFα could also be partially explained by the common denominator governing their production, i.e., the triggering of the malignancy-induced immunologic response.

The present study showed that IL-6, TNFα and CRP levels definitely increase in CRC patients. Although earlier observations of the IL-6 relation to disease stage were not fully replicated here, the current study in a Greek population adds to the growing evidence that IL-6 and CRP preoperative serum concentrations are correlated to decreased patients' overall survival. Such markers could be considered as appropriate predictors of CRC patients' prognosis and, to a certain extent could provide valuable information when determining treatment strategies.

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